ORIGINAL ARTICLE

Host factors and genetic susceptibility to infections due to intracellular bacteria and fastidious organisms

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Abstract

While genetic polymorphisms play a paramount role in tuberculosis (TB), less is known about their contribution to the severity of diseases caused by other intracellular bacteria and fastidious microorganisms. We searched electronic databases for observational studies reporting on host factors and genetic predisposition to infections caused by intracellular fastidious bacteria published up to 30 May 2014. The contribution of genetic polymorphisms was documented for TB. This includes genetic defects in the mononuclear phagocyte/T helper cell type 1 (Th1) pathway contributing to disseminated TB disease in children and genome-wide linkage analysis (GWAS) in reactivated pulmonary TB in adults. Similarly, experimental studies supported the role of host genetic factors in the clinical presentation of illnesses resulting from other fastidious intracellular bacteria. These include IL-6 -174G/C or low mannose-binding (MBL) polymorphisms, which are incriminated in chronic pulmonary conditions triggered by *C. pneumoniae*, type 2-like cytokine secretion polymorphisms, which are correlated with various clinical patterns of *M. pneumoniae* infections, and genetic variation in the NOD2 gene, which is an indicator of tubal pathology resulting from *Chamydia trachomatis* infections. Monocyte/macrophage migration and T lymphocyte recruitment defects are corroborated to ineffective granuloma formation observed among patients with chronic Q fever. Similar genetic polymorphisms have also been suggested for infections caused by *T. whipplei* although not confirmed yet. In conclusion, this review supports the paramount role of genetic factors in clinical presentations and severity of infections caused by intracellular fastidious bacteria. Genetic predisposition should be further explored through such as exome sequencing.

Keywords: *C. burnetii*, *C. psittaci*, *C. trachomatis*, genotyping, host genetics, intracellular bacteria, *M. pneumoniae*, molecular diagnosis, Mycobacteria, risk factors, *T. whipplei*
Original Submission: 15 August 2014; **Revised Submission:** 24 October 2014; **Accepted:** 24 October 2014
Article published online: 3 November 2014
Clin Microbiol Infect 2014; **20**: 1246–1253
10.1111/1469-0691.12806

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Introduction

Infections caused by intracellular bacteria and fastidious organisms such as *Chlamydia, Mycoplasma* and *Coxiella burnetii* are associated with important morbidities [1]. Although most of these infections are prevalent worldwide [2], variability in prevalence may be related to ecological vectors such as ticks and mosquitoes for diseases caused by Rickettsiae or Tularemia. Socio-demographical factors such as farming and close contact with animals are also important risk factors as documented in multiple outbreaks of *C. burnetii* infections reported after close exposure to animals in the Netherlands between 2007 and 2011 [3] and more recently in Switzerland [4]. Variability in the clinical expression may also result from bacterial virulence factors present in a given strain, the extent of exposure (inoculum) or host factors such as genetic susceptibility. Likewise, variability in morbidities and mortality can be explained by socio-economic factors, mainly access to medical facilities, which has a direct impact on time to diagnosis and treatment. Transmission route and host factors such as genetic

susceptibility may also be important. While the contribution of socio-demographic factors and arthropod or animal vectors to infections caused by intracellular bacteria and fastidious organisms is well documented, less is known about the role of host factors such as genetic polymorphisms. Thus, this review will specifically focus on genetic susceptibility to infections caused by intracellular bacteria and fastidious organisms.

Literature Search

We included observational studies reporting on host factors and genetic susceptibility to infections caused by intracellular organisms and fastidious bacteria such as chlamydiae (*C. trachomatis, C. psittaci* and *C. pneumoniae*), *M. pneumoniae, C. burnetii* and *T. whipplei*. In addition, observational studies focusing on human genetics of tuberculosis were included as host factor susceptibility to *Mycobacterium tuberculosis* infections was extensively described. Given the complexity of human genetics of tuberculosis and the recent publication of an extensive review [5], we will provide a brief overview of genetic susceptibility to mycobacterial infections

Practically, we searched MEDLINE and EMBASE for relevant studies published in any year or in any language up to 30 May 2014. We also reviewed references listed in key articles. More than 150 unique records were initially identified through our literature search (Table 1).

Mycobacterium tuberculosis

Tuberculosis remains a major public health problem, with 8.7 million new cases diagnosed each year [6,7]. Although one-third of the world's population is exposed to TB, not all the individuals will become infected. Among those infected, only about 5% will develop clinical disease, thus strongly suggesting the role of underlying genetic factors in TB. The observations of increased prevalence of extra-pulmonary tuberculosis among non-Caucasian populations [8] and increased concomittant rates of TB disease among monozygote twins (60%) vs dizygotes twins (35%) [9] support a major role for human genetic factors in the development of TB (Table 2). Recent documentation of high variability rates of tuberculin skin test (TST) responsiveness and quantitative Interferon Gamma Release Assay (IGRA) reactivity following exposure to active TB cases in healthy children [10,11] supports the role of host factors. Genetic polymorphism may have an impact on the type of histopathological lesions observed (granuloma vs disseminated disease) as well as on clinical disease (pulmonary vs extrapulmonary disease) and morbidity rates.

Genetic variants correlated with susceptibility to TB include *Il10* promoter haplotypes and genome-wide linkage analysis (GWAS). Increased rates of an *Il10* promoter haplotype resulting in low levels of circulating Il-10 were documented among TST-positive subjects compared with TST-negative ones [12], whereas GWAS correlated specific chromosomal regions (2q21-2q24 and 5p13-5q22) with persistent TST negativity [13].

While severe primary TB commonly occurs in children under 2 years of age, only a minority of infected children will develop severe clinical forms, thus supporting the role of single inborn errors of immunity. Indeed, monogenic Mendelien defects in the mononuclear phagocyte/T helper cell type 1 (Th1) pathway were documented in up to 40% of children with disseminated primary TB [7]. Among these, primary immunodeficiencies resulting from mutations in several genes, such as complete IFNGR1, IFNGR2, IL12B, IL12BR1, STAT1, IRF8 and

TABLE 1. Documented genetic polymorphisms and host factors predisposing to infections due to intracellular bacteria

Pathogens	Population	Documented polymorphisms or host factors
Mycobacterium tuberculosis	Adults and children	MSMD (IFNGR1, IFNGR2, IL12B, IL12BR1, STAT1, IRF8, ISG15 receptor defects) HLA (HLA-DR2, HLA-DQB1) TLR1, TLR2 VDR NRAMP1 (alias SLC11A1) GWAS
Chlamydia pneumoniae, Chlamydia psittaci	Adults	Il-6-174G/C Low-mannose binding (MBL)-2 Immunity-related GTP-ases (IRGs)
Chlamydia trachomatis	Adults and children	Pathogen recognition: TLRs (2,4,9), NODs (1,2), CD14, CCR5, CXCR5, MBL/MBP Cytokines: ILs (1β, 1RN, 2, 4, 4R, 6, 10, 12B), IFNγ, TNFα, TGF-β, LTA Other: HLA (A, B, C, CW, DQA, DQB, DR), MMP9, IκBα, IκBL, TRAILR1
Mycoplasma pneumoniae	Children	Il-4 levels Ratio Il-4/IFN-γ
Coxiella burnetii	Adults	Il-10 overproduction leading to defective monocyte and phagosome maturation
T. whipplei	Adults	Decreased Th1 and Th17 reactivity

MSMD, Mendelian susceptibility to mycobacterial disease; HLA, human leucocyte antigen; TLR1, TLR2, Toll-like 1 and 2 receptors; VDR, vitamin D receptor; NRAMP1 (alias SLC11A1), specific macrophage protein 1 (NRAMP1) gene polymorphisms; GWAS, genome-wide linkage analysis; Il, interleukin; IFN, interferon.
No documented polymorphism/host factors for *Bartonella spp.*

TABLE 2. Characteristics of the most important observational studies included in the review of *Mycobacterium tuberculosis*

Author	Year	Country	Population	Polymorphisms
Boisson-Dupuis *et al.* [15]	2011	France	Children	Il-12Rβ1 deficiency
Gao *et al.* [20]	2010	China	Adults	VDR polymorphism: *Fok*I ff genotype, *Bsm*I bb genotype, *Taq*1, *Apa*I
Li *et al.* [25]	2006	China	Adults	NRAMP1 (alias SLC11A1)
Malik *et al.* [26]	2005	Canada	Adults and children	NRAMP1 (alias SLC11A1)
Greenwood *et al.* [33]	2000	Aboriginal Canadians	Adults and children	NRAMP1 (alias SLC11A1)
Ma *et al.* [22]	2007	UK	Adults	TLR1, TLR2
Vejbaesya *et al.* [23]	2002	Thailand	Adults	HLA (HLA-DR2, HLA-DQB1)
Thye *et al.* [30]	2010	Ghana, Gambia	Adults and children	GWAS: chromosome 18q11.2

Nb, number; MSMD, Mendelian susceptibility to mycobacterial disease; HLA, human leucocyte antigen; TLR1, TLR2, Toll-like 1 and 2 receptors; VDR, vitamin D receptor; NRAMP1 (alias SLC11A1), specific macrophage protein 1 (NRAMP1) gene polymorphisms; Il, interleukin; IFN, interferon; GWAS, genome-wide linkage analysis.

ISG15IL, were documented in children with disseminated TB disease [14–17]. Polygenic somatic and germinal mutations, such as HLA polymorphisms (HLA-DR2 and HLA-DQB1), as well as mutations in Toll-like 1 and 2 receptors (TLR1, TLR2) and genes coding for the vitamin D receptor (VDR) may be incriminated in reactivated pulmonary TB in adults, although no convincing evidence has been provided so far [18–23]. In contrast, various studies supported the role of specific macrophage protein 1 (NRAMP1) gene polymorphisms in pulmonary TB, with a heterogenous effect across populations (African, Asian populations vs European populations), epidemiological settings, clinical phenotypes and age at onset of TB [24]. A recent meta-analysis [24] correlated NRAMP1 polymorphisms with pulmonary TB in African and Asian populations but not those of European descent [25,26]. A stronger genetic effect associated with early-onset disease was supported by the documentation of numerous NRAMP1 alleles in children whereas only a few were recovered from adult patients [26]. Early-onset pulmonary TB was also associated with variants of the TOX gene involved in the development of CD4+ T cells [27–29].

A recent GWAS conducted among populations from Gambia and Ghana identified a 'gene desert' on chromosome 18 as a risk factor for pulmonary TB and a second locus on chromosome 11p13 as protective against TB [30]. These associations were not consistent when repeated in other populations [31,32], thus suggesting that GWAS may have a limited impact on predisposition to adult pulmonary TB, at least when considered as a single phenotype. In conclusion, the exact nature of genetic factors involved in TB remains unknown. Genetic heterogeneity together with a complex mode of inheritance and other factors such as the intensity of exposure to TB and variable *M. tuberculosis* strain virulence may also have an impact on the clinical course of TB [26,33].

Chlamydia trachomatis

Genetic polymorphism may also affect clinical outcomes resulting from infections due to intracellular bacteria and other fastidious organisms such as *Chlamydia* spp. The genus *Chlamydia* comprises three important human pathogens. *C. trachomatis* causes blinding trachoma [34–36] and sexually-transmitted infections, whereas *Chlamydia pneumoniae* is associated with asthma and community-acquired pneumonia [37] and *Chlamydia psittaci* may cause severe respiratory systemic zoonotic infections [36].

Host genetic markers seem to be the most promising biological indicators of complicated chlamydia infection at present [38–47]. Recent studies have led the way in identifying genetic biomarkers useful for distinguishing women with a past chlamydia infection and higher probability of developing complications from women with an uncomplicated chlamydia infection cleared without late complications. The relevance of studying host genetic markers as well as behavioural markers linked to acquiring chlamydia infection has been shown by recent research on *C. trachomatis* strains that cause trachoma. Bailey *et al.* [47] found that up to 40% of the host-response to chlamydia infection in Gambian twin pairs is based on host genetics. They estimated the relative contribution of host genetics within the total variation in lymphoproliferative responses (specific T-cell immune responses) to *C. trachomatis* antigen. The scarring of the cornea (trachoma) and the scarring of the fallopian tubes (sexually transmitted chlamydia infection) have a remarkable immunogenetic similarity. This has been summarized in a recent review [40] which documented identical single nucleotide polymorphisms (SNPs) in ocular and tubal scarring for such as IL-10, TNF-alpha and HLA types. In addition, mannose-binding lectin gene polymorphism (MBL) has previously been described for ocular scarring.

SNP biomarkers have already shown a high predictive value for the development of tubal pathology after being exposed to *Chamydia trachomatis*. Thus, MBL was also associated with tubal pathology development. Recent work explored whether genetic traits (carrying multiple SNPs in different genes) in the bacterial sensing system are associated with an aberrant immune response and subsequently with tubal pathology following a *C. trachomatis* infection. In one of those studies the authors assessed in sub-fertile women the

presence of five single nucleotide polymorphisms (SNPs) in five genes, all encoding for pattern recognition receptors (PRRs) involved in sensing bacterial components. The SNPs were chosen based on functional consequences they had for these genes; for instance, the genetic variation in the NOD2 gene resulted in a shorter protein due to a stop codon introduced by the SNP. It was shown that sub-fertile women with serological evidence of prior chlamydia infection (IgG) and two or more of these SNPs had a significantly higher chance of developing pathology than women with fewer or no SNPs [40]. This study shows the potential of host genetic markers as indicators of the risk of late complications from chlamydia infection in women. This type of biomarker could be applied in better triage of women screened by the gynaecologist for subfertility and laparoscopy (Fig. 1) [38].

Recently, at the Thirteenth International Symposium on Human Chlamydial Infections (June 2014), two preliminary key studies were presented. The first by Roberts and colleagues [A] used for the first time a genome wide association study (GWAS) to scan for pathway-wide genomic differences between cases of scarring trachoma and controls. Based on the polygenic character of infectious diseases, meaning that each gene contributes a small proportion of the overall heritability, they used pathway of distinction analysis (PODA) to test for associations between groups of SNPs, focusing on functional genes and gene-to-pathway associations. The top 15 SNPs had p-values between 10E-8 and 10E-5. By gene ontology (GO) analyses, many pathways were identified, from which the most prominent were pathways related to mitosis, the microtubale cytoskeleton, cell-cell junctions and hormone-mediated signalling. The ongoing study will be extended by validation in a second case-control cohort, further *in vitro* analysis and system biology-based analyses.

The second study was presented by Byrne and colleagues [B]. They worked with an accurate forward genetic tool by using an advanced recombinant inbred mouse strain set to identify sets of genes associated, among others, with upper genital tract complications. Oviduct disease severity was linked to 17 candidate genes on chromosome 3 of mice, showing synteny in part with orthologous genes on human chromosome 1. Similar results were obtained with 19 candidate genes on mouse chromosome 19, showing synteny in part with orthologous genes on human chromosome 9. The use of this advanced recombinant inbred mouse is a major new tool to help discovery of genes linked to susceptibility to and severity of *C. trachomatis* disease.

All the above findings in the field of immunogenetics, genetics and genomics of *C. trachomatis* infections are of high relevance for public health and healthcare in general

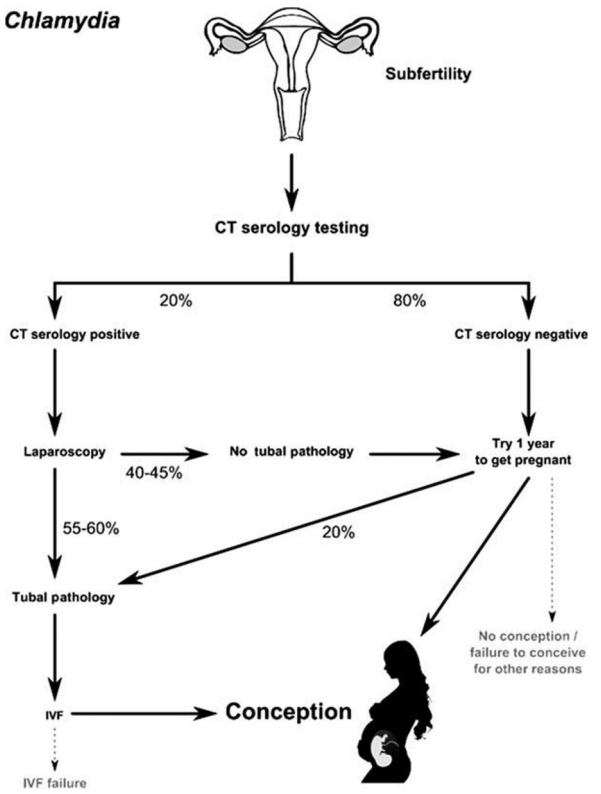

FIG. 1. Triage of women screened by a gynaecologist for subfertility and laparoscopy, with stars indicating decision points where host genetic markers for a high risk of development of complications from *Chlamydia trachomatis* infection could be applied. A good SNP trait in combination with IgG CT+ could indicate no laparoscopy is indicated (green bar), while a bad SNP trait and IgG CT- could mean a laparoscopy is indicated (red bar). The SNP trait will have a 'grey' zone (grey bar) in which no clear advice can be given, and the gynaecologist has to decide based on the available clinical data.

[39,41]. These results will contribute to the understanding of chlamydial infection, which is strongly associated with ectopic pregnancy, tubal infertility, pelvic inflammation and miscarriage [48]. Furthermore, these findings provide new insights into the pathways that help explain individual heterogeneity in the clinical course of *C. trachomatis* infection and the possible development of more targeted and personalized approaches in the prevention, diagnosis and treatment of disease, especially in subfertility diagnosis.

C. pneumoniae and *C. psittaci*

Chlamydia pneumoniae may result in a wide spectrum of acute respiratory conditions such as community-acquired pneumonia (CAP), bronchitis [49,50] and pharyngitis. Recent evidence also suggests its association with chronic conditions such as chronic

obstructive pulmonary disease (COPD), cystic fibrosis (CF) [51] and asthma exacerbations [52,53], thus raising the question of underlying host genetic susceptibility [50].

Indeed, recent *in vitro* studies suggested the role of underlying genetic factors such as IL-6 -174G/C or low mannose-binding (MBL) polymorphisms in the development of chronic pulmonary conditions triggered by *C. pneumoniae* [54,55]. Therefore, host factors may determine the nature of *C. pneumoniae* infections (acute vs. chronic).

Chlamydia psittaci is associated with life threatening respiratory infections. The contribution of genetic polymorphism to susceptibility to *C. psittaci* infections has recently been supported by the documentation of polymorphisms in the family of immunity-related GTP diseases (IGR) in animal models [35]. Thus, genetic polymorphism may have an impact on the susceptibility to infections caused by both *Chlamydia pneumoniae* and *psitacci,* as well as the nature of the respiratory disease. These findings should, however, be confirmed by using new exome sequencing strategies and should be validated in a large cohort of patients. Similar investigations should be carried out in respiratory conditions resulting from *M. pneumoniae* infections, especially given its frequent documentation in CAP in children.

Mycoplasma pneumoniae

Mycoplasma pneumoniae infections are associated with a wide spectrum of clinical entities, including mainly conjunctivitis and respiratory diseases [56,57]. It is the most prevalent agent of CAP in children above 2 years of age and has also been associated with asthma exacerbations [52,53,58–60], recurrent wheezing episodes and acute bronchitis in children [57,58]. More recent evidence suggests its role in CF exacerbations [61]. As such, children presenting with these conditions should systematically be screened for *M. pneumoniae* in addition to viral pathogens which are usually considered as the main triggers for CF. In addition, *M. pneumoniae* has also been associated with immune-mediated conditions [62–65], resulting in erythema multiforma and reactive arthritis.

In vitro studies [62,63,65] have demonstrated that *M. pneumoniae*-infected epithelial cells resulted in the induction of various cytokines and chemokines, including pro-inflammatory (tumour necrosis factor-α), type 1 (interferon-γ) and type 2 (interleukin-6) cytokines and α (interleukin-8) and β-chemokines [63]. In summary, a predominant type 2-like cytokine response results from *M. pneumoniae* infections, as supported by experimental studies [65,66]. Thus, individuals with stronger cytokine and cell-mediated immune responses may experience more severe pulmonary injury, thus supporting the contribution of genetic polymorphisms [67,68].

Coxiella burnetii

Another agent of atypical pneumonia is *C. burnetii,* for which there is more evidence of the importance of underlying host polymorphisms. *Coxiella burnetii*, an obligate intracellular bacterium, is the causal agent of Q fever. It is prevalent worldwide and highly infectious [2,69], being mainly transmitted by inhalation of contaminated aerosols [70]. Infection generally results in acute Q fever, which is symptomatic in <40% of cases [2]. A small proportion (<5%) will present with severe disease such as atypical pneumonia or granulomatous hepatitis. Less frequently, pericarditis, meningo-encephalitis or arthritis may also occur [1]. Chronic Q fever, mainly endocarditis, observed among individuals with underlying predispositions (pregnancy, immunosuppression or valvular defects), occurs months to years after the acute episode and can result in significant mortality rates (25–60%) [1]. Auto-immune conditions such as Libman-Sacks endocarditis have been reported in patients with documented *C. burnetii* infections [71]. The highest rates of symptomatic Q fever are observed among men and children above 15 years of age [72], suggesting a major role for human genetic factors [73]. A more recent, a more recent study [4] reported cases of hepatitis that resulted from exposure to aerosols, thus reinforcing the contribution of other factors such as host-related factors.

Immune control of *C. burnetii* results in granuloma formation and systemic cell-mediated immune responses, including IFN-γ- production, probably as a result of monocyte/macrophage migration and T lymphocyte recruitment [74–76]. Experimental studies have correlated defective monocyte migration [74] and defective phagosome maturation resulting from Il-10 overproduction [75,76] with ineffective granuloma formation, a phenotype observed among patients with chronic Q fever. These experimental findings strongly support the contribution of underlying genetic polymorphisms.

Tropheryma whipplei

Like *Coxiella, Tropheryma whipplei* is an important agent of blood culture-negative endocarditis. *T. whipplei* is generally acquired through faeco-oral transmission. While *T. whipplei* is found ubiquitously in the environment, it remains a rare disease with an annual incidence below 1 per 1 000 000 population [77–79], suggesting the role of host factors. Furthermore, a higher prevalence of the bacteria is reported in men of European ancestry [78]. Also, *T. whipplei* can be detected in as many as 35% of healthy carriers, thus reinforcing the role of an underlying polymorphism in determining late

disease onset [80]. The contribution of a genetic background to the evolution of Whipple disease was recently supported by the association of Whipple disease with human leukocyte antigen alleles DRB1*13 and DQB1*06 [79,81,82]. A genetic polymorphism in the cytokine genes was supported by the documentation of low levels of TGF-β1 and high production of Il-10, resulting in decreased Th1 and Th17 reactivity among infected patients compared with healthy controls, although the association was not significant [83]. Polymorphisms in the cytokine genes should be further explored in larger cohorts, ideally by exome sequencing.

Conclusion

Infectious diseases due to intracellular and/or fastidious bacteria may have pleomorphic clinical presentations, partially due to inter-individual variation in terms of polygenic genetic susceptibility. To date, most gathered information has been hypothesis driven. Thus, in the coming years, with the use of exome sequencing, a new unexpected genetic locus might be discovered.

Funding source

No funding source provided.

Financial Disclosure

The authors have no financial relationships relevant to this article to disclose.

Transparency Declaration

The other authors have no conflicts of interest to disclose.

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Preliminary Key studies

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